AF

Docket No.: 480821.90043

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Date of Signature and Deposit: June 23, 2005

Richard T. Roche, Reg. No. 38,599

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

Applicants:	Jan Tadeusz Czernuszka *et al.*
Application No.:	09/720,411
Filing date:	March 12, 2001
Title:	CALCIUM PHOSPHATE COATED VESICLES
Art Unit:	1615
Examiner:	Gollamudi Kishore

SUBMISSION OF APPELLANTS' BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants hereby submit three copies of their brief in the appeal of the final rejection of the above-identified application. Also attached is a request for a four month extension to extend the deadline to June 23, 2005.

The $500 fee for filing a brief and the four month extension fee of $1590 should be charged to Deposit Account No. 17-0055. A duplicate copy of this paper is enclosed for this purpose.

Respectfully submitted,

Dated: June 23, 2005

By: _____

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APPELLANTS' BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants, Jan Tadeusz Czernuszka and David Bryan Haddow, having filed a timely Notice of Appeal in the above-identified patent application, hereby submit this brief. Appellants reserve the right to request telephonic or other oral hearing.

1. Real Party in Interest

ISIS Innovation Limited, a British body corporate, assignee of record.

2. Related Appeals and Interferences

None.

3. Status of the Claims

Claims 1-2, 6-12, 14-16, 18-23, 26-30 and 35-38 are pending, have been finally rejected, and are being appealed. Claims 3-5, 13, 17, 24-25 and 31-34 have been canceled.

4. Status of Amendments

No amendments have been made after final rejection.

5. Summary of Invention

The present invention relates to vesicles comprising an inner layer which comprises a phospholipid, an outer layer which comprises calcium phosphate, and a pharmaceutically active compound contained within the vesicle. Among other things, the vesicles can be used for drug delivery.

Independent claim 1 recites a vesicle comprising an inner layer which comprises a phospholipid as at page 2, line 17 of the specification, an outer layer which comprises calcium phosphate where the outer layer is formed on the inner layer as at page 2, line 18 and page 4, lines 17-18 of the specification, and a pharmaceutically active compound contained within the vesicle as at page 2, line 27-28 of the specification.

Dependent claim 2 specifies that the phospholipid is selected from L-α-phosphatidylcholine and L-α-phosphatidylserine as at page 2, lines 21-22 of the specification.

Dependent claim 6 specifies that the outer layer further comprises ions selected from carbonate. hydrogen phosphate, chloride, fluoride or magnesium as at page 4, lines 27-30 of the specification.

Dependent claim 7 specifies that the thickness of the outer layer is from 5 to 50 nm. as at page 5, line 15 of the specification.

Dependent claim 8 specifies that the thickness of the outer layer is from 5 to 20 nm. as at page 5, line 16 of the specification.

Dependent claim 9 specifies that the thickness of the outer layer is about 10 nm. as at page 5, line 12 of the specification.

Dependent claim 10 specifies that the size of the vesicle is from 100 nm to 10 μm. as at page 6, line 5 of the specification.

Dependent claim 11 specifies that the size of the vesicle is at least 300 nm. as at page 6, line 5 of the specification.

Dependent claim 12 specifies that the size of the vesicle is at least 1 μm as at page 6, line 6 of the specification.

Dependent claim 14 specifies that the pharmaceutically active compound assists the binding of the outer layer to bone, treats a specific bone disease or any diseased region adjacent to bone, or relieves pain as at page 2, lines 27-30 of the specification.

Dependent claim 15 specifies that the pharmaceutically active compound is selected from parathyroid hormone, vitamin D derivatives, bisphosphanates, bone morphogenetic proteins, analgesics, ^{32}P or ^{89}Sr containing compounds, indomethacin, prostoglandins, interleuken 6 inhibitors and antibiotics as at page 3, lines 4-8 of the specification.

Dependent claim 16 specifies a process for preparing a vesicle as claimed in claim 1 where the process comprises a) forming a vesicle in an aqueous mixture comprising a phospholipid and a pharmaceutically active compound, and b) calcifying the outer surface of the vesicle by contacting said vesicle with an aqueous solution comprising calcium and phosphate ions as at page 3, lines 9-12 and page 4, lines 10-11 of the specification.

Dependent claim 18 specifies a process for preparing a vesicle as claimed in claim 16 where the aqueous mixture further comprises an alcohol as at page 4, lines 4-9 of the specification.

Dependent claim 19 specifies a process for preparing a vesicle as claimed in claim 18 where the alcohol is selected from methanol, ethanol, propanol and butanol as at page 4, lines 4-9 of the specification.

Dependent claim 20 specifies a process for preparing a vesicle as claimed in claim 18 where the concentration of alcohol is no more than 10% by volume of the aqueous mixture as at page 4, lines 4-9 of the specification.

Dependent claim 21 specifies a process for preparing a vesicle as claimed in claim 16 where the ratio of calcium to phosphate ions in the aqueous solution is from 1:1 to 2:1 as at page 4, line 19 of the specification.

Dependent claim 22 specifies a process for preparing a vesicle as claimed in claim 21 where the ratio of calcium to phosphate ions is 1.4:1 to 2:1 as at page 4, line 20 of the specification.

Dependent claim 23 specifies a process for preparing a vesicle as claimed in claim 22 where the ratio of calcium to phosphate ions is about 1.5:1 as at page 4, line 20 of the specification.

Dependent claim 26 specifies a solid substrate wherein regions of said substrate have attached thereto a layer comprising vesicles as claimed in claim 1 with other region or regions having no vesicles attached thereto as at page 6, lines 10-14 of the specification.

Dependent claim 27 specifies a substrate according to claim 26 which comprises a surface layer comprising electrically conducting and non-conducting regions with a layer comprising vesicles on the conducting regions as at page 6, lines 15-20 of the specification.

Dependent claim 28 specifies a substrate according to claim 27 wherein the non-conducting regions are from 10 μm to 2 mm in size as at page 6, line 19 of the specification.

Dependent claim 29 specifies a substrate according to claim 28 wherein the non-conducting regions are about 150 μm in size as at page 6, line 20 of the specification.

Dependent claim 30 specifies a process for preparing a substrate according to claim 26 which process comprises electrolytically depositing the coating comprising vesicles onto the conducting regions of the substrate as at page 6, lines 21-23 of the specification.

Dependent claim 35 specifies a method of treating a bone disorder in a patient which comprises implanting in the patient a substrate as claimed in claim 26 as at page 6, lines 10-14 of the specification.

Dependent claim 36 specifies a method of delivering pharmaceutically active compounds to a patient which comprises implanting in the patient a substrate as claimed in claim 26 comprising one or more pharmaceutically active compounds as at page 6, lines 10-14 of the specification.

Dependent claim 37 specifies a vesicle according to claim 1 wherein the pharmaceutically active compound is an antibiotic as at page 3, line 7 of the specification.

Dependent claim 38 specifies a process according to claim 16 wherein the said aqueous solution is supersaturated as at page 6, lines 30-31 of the specification.

6. Issues

1. Claims 1-2, 6-12, 14-16, 18-23, 26-29 and 35-38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over EP-0-479,582 in combination with either of Eanes (Bone and Mineral 17, pp. 269-272, 1992; or Calcif. Tissue Int. 40, pp. 43-48, 1987) and U.S. 5,039,546 to Chung; and claims 26-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over EP-0-479,582 in combination with either of Eanes (Bone and Mineral 17, pp. 269-272, 1992; or Calcif. Tissue Int. 40, pp. 43-48, 1987) and U.S. 5,039,546 to Chung in further view of U.S. 5,310,464 to Redepenning.

7. Grouping of Claims

Claims 1-2, 6-12, 14-16, 18-23, 26-30 and 35-38 can be grouped together for purposes of this appeal with claim 1 being a representative claim.

8. Arguments

The final Office Action does not provide sufficient evidence which would reasonably support a conclusion that the subject matter of claims 1-2, 6-12, 14-16, 18-23, 26-30 and 35-38 would have been *prima facie* obvious within the meaning of 35 U.S.C. 103(a).

First, attention is directed to *In re Hoeksema*, 399 F.2d 269 (CCPA 1968) in which the court answered the question whether a claimed compound may be said to be legally obvious when no process for making the compound is shown in the prior art relied upon. The court first stated that "the invention as a whole is the compound and a way to produce it." 399 F.2d at 273 (Underlining added). The court then stated that

> it is our view that if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds. 399 F.2d at 274.

After setting forth this standard, the court reviewed an affidavit filed by the applicant which pointed out as a fact that the prior art reference did not disclose a process for producing the different compounds claimed. The affidavit as quoted in the *In re Hoeksema* case did not include any experimental data. The court concluded that the affidavit stated facts which were legally sufficient to overcome the position of the Patent Office as to the legal effect under section 103 of the prior art reference. In particular, the court noted that the affidavit pointed out that there is no indication in the reference that the process used to produce the prior compounds could be used to produce applicant's compounds. The court concluded that "since we are of the view that the method for making the compounds is an integral part of the 'invention as a whole' which we must consider under section 103, we conclude that the burden of going forward with proofs to support its position as to obviousness of the claimed invention shifted to the Patent Office upon [applicant's] filing of the [named] affidavit." 399 F.2d at 275.

Now turning to the present application, the Inventor's Declaration in Appendix B was submitted with a Request for Continued Examination filed October 7, 2003. The Inventor's Declaration makes it clear that the process of the prior art references could not produce the invention of claim 1. In particular, it was explained that the processes of Eanes (Bone and Mineral 17, pp. 269-272, 1992; or Calcif. Tissue Int. 40, pp. 43-48,

1987) would puncture the walls of the vesicle thereby making the containment of a pharmaceutically active agent within the vesicle (as recited in claim 1) impossible.

Under the standards of the *In re Hoeksema* case detailed above, the present Applicants have met their burden of overcoming the initial obviousness position of the Patent Office. In other words, the Applicants have provided sufficient scientific evidence that a method for making the compounds is not obvious from the prior art. Having met their burden of overcoming the initial obviousness position of the Patent Office with the Inventor's Declaration of Appendix B, it is submitted that the Patent Office is now required to come forth with a convincing line of reasoning based on scientific evidence that refutes the Inventor's Declaration of Appendix B. See *In re Hoeksema,* 399 F.2d at 275.

In the final Office Action, a response to the Applicants' evidence in the form of the previously entered Inventor's Declaration of Appendix B states

> Applicant argues that the declaration makes it clear that the process of prior art references could not produce the invention of claim 1 and in particular, the processes of Eanes would puncture the walls of the vesicles thereby making the containment of a pharmaceutically active agent within the vesicle impossible. This argument is not found to be persuasive since there is nothing in Eanes to indicate that the hydroxy apatite, which is outside made the entrapped antibiotic to leak out. Since applicant is questioning the teachings of the prior art, the burden is therefore upon applicant to show that the entrapped antibiotic leaks out because the process is different and applicant has not provided any experimental evidence to dispute the teaching of the prior art. Secondly, as previously pointed out, instant claims do not recite any specific amounts of the active agent encapsulated in the vesicles.

It is believed that this quoted language fails to refute the Inventor's Declaration of Appendix B in that it concludes that "the burden is therefore upon applicant to show that

the entrapped antibiotic leaks out because the process is different and applicant has not provided any experimental evidence to dispute the teaching of the prior art."

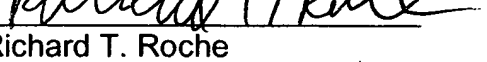
In this regard, the Inventor's Declaration describes how in the process of Eanes, calcium *penetrates the walls of the vesicles* and acts as a seed for the formation of calcium phosphate such that the punctured walls leak. Thus, the Inventor's Declaration has met the burden of showing how the prior process is different. With respect to the request for experimental data, the affidavit of *In re Hoeksema* did not include experimental data (see *In re Hoeksema,* 399 F.2d at 271 n.6) and therefore, there does not appear to be a basis for the Patent Office requiring experimental data. Finally, the comment that the claims do not recite any specific amounts of the active agent encapsulated in the vesicles does not serve to refute the Inventor's Declaration.

In summary, the present Applicants have met their burden of overcoming the initial obviousness position of the Patent Office with the previously entered Inventor's Declaration and the Patent Office has failed to come forth with a convincing line of reasoning based on scientific evidence that refutes the Inventor's Declaration. Because the Patent Office has failed to come forward with further rebuttal evidence of obviousness, the Appellants request reversal of the final rejection in the application.

Respectfully submitted,

Jan Tadeusz Czernuszka *et al.*

Dated: June 23, 2005

By: 

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APPENDIX A

Copy of Claims Involved in Appeal

1. A vesicle comprising:

a) an inner layer which comprises a phospholipid, and

b) an outer layer which comprises calcium phosphate, the outer layer being formed on the inner layer; and

c) a pharmaceutically active compound contained within the vesicle.

2. A vesicle according to claim 1 wherein the phospholipid is selected from L-α-phosphatidylcholine and L-α-phosphatidylserine.

6. A vesicle according to claim 1 wherein the outer layer further comprises ions selected from carbonate. hydrogen phosphate, chloride, fluoride or magnesium.

7. A vesicle according to claim 1 wherein the thickness of the outer layer is from 5 to 50 nm.

8. A vesicle according to claim 7 wherein the thickness of the outer layer is from 5 to 20 nm.

9. A vesicle according to claim 8 wherein the thickness of the outer layer is about 10 nm.

10. A vesicle according to claim 1 wherein the size of the vesicle is from 100 nm to 10 μm.

11. A vesicle according to claim 10 wherein the size of the vesicle is at least 300 nm.

12. A vesicle according to claim 11 wherein the size of the vesicle is at least 1 μm.

14. A vesicle according to claim 1 wherein the pharmaceutically active compound assists the binding of the outer layer to bone, treats a specific bone disease or any diseased region adjacent to bone, or relieves pain.

15. A vesicle according to claim 14 wherein the pharmaceutically active compound is selected from parathyroid hormone, vitamin D derivatives, bisphosphanates, bone morphogenetic proteins, analgesics, ^{32}P or ^{89}Sr containing compounds, indomethacin, prostoglandins, interleuken 6 inhibitors and antibiotics.

16. A process for preparing a vesicle as claimed in claim 1, which process comprises

a) forming a vesicle in an aqueous mixture comprising a phospholipid and a pharmaceutically active compound, and

b) calcifying the outer surface of the vesicle by contacting said vesicle with an aqueous solution comprising calcium and phosphate ions.

18. A process according to claim 16 wherein the aqueous mixture further comprises an alcohol.

19. A process according to claim 18 wherein the alcohol is selected from methanol, ethanol, propanol and butanol.

20. A process according to claim 18 wherein the concentration of alcohol is no more than 10% by volume of the aqueous mixture.

21. A process according to claim 16 wherein the ratio of calcium to phosphate ions in the aqueous solution is from 1:1 to 2:1.

22. A process according to claim 21 wherein the ratio of calcium to phosphate ions is 1.4:1 to 2:1.

23. A process according to claim 22 wherein the ratio of calcium to phosphate ions is about 1.5:1.

26. A solid substrate wherein regions of said substrate have attached thereto a layer comprising vesicles as claimed in claim 1 with other region or regions having no vesicles attached thereto.

27. A substrate according to claim 26 which comprises a surface layer comprising electrically conducting and non-conducting regions with a layer comprising vesicles on the conducting regions.

28. A substrate according to claim 27 wherein the non-conducting regions are from 10 μm to 2 mm in size.

29. A substrate according to claim 28 wherein the non-conducting regions are about 150 μm in size.

30. A process for preparing a substrate according to claim 26 which process comprises electrolytically depositing the coating comprising vesicles onto the conducting regions of the substrate.

35. A method of treating a bone disorder in a patient which comprises implanting in the patient a substrate as claimed in claim 26.

36. A method of delivering pharmaceutically active compounds to a patient which comprises implanting in the patient a substrate as claimed in claim 26 comprising one or more pharmaceutically active compounds.

37. A vesicle according to claim 1 wherein the pharmaceutically active compound is an antibiotic.

38. A process according to claim 16 wherein the said aqueous solution is supersaturated.

APPENDIX B

Evidence

Copy of Previously Entered Inventor's Declaration

OxfordMaterials

In the Matter of US Patent Application
Serial Number 09/720,411 CZERNUSZKA et al.

DECLARATION

I, JAN TADEUSZ CZERNUSZKA, declare as follows:-

1. I am a British citizen employed by the University of Oxford, Department of Materials, Parks Road, Oxford, OX1 3PH and I am the first named inventor of the above referenced application.

2. Since 1996 I have been a University lecturer at the Department of Materials, University of Oxford and a Fellow and Tutor in Materials at Trinity College, Oxford. I possess a BSc. (Hons), ARSM in Materials Science from Imperial College, London, an MA from the University of Oxford and a Ph.D from the Department of Metallurgy and Materials Science, University of Cambridge. I have published over 100 articles on biomaterials, material and microscopy and related areas.

3. I have been asked to review the procedure used by E. D. Eanes to prepare vesicles as discussed in Calcified Tissue International (1987) 40: 43-48 and Bone and Mineral 17 (1992) 269-272 .

4. Eanes prepares vesicles using a phospholipid, typically phosphatidycholine. Put briefly, a mixture of the lipid was buffered with phosphate and then rotary-evaporated. Liposomes (also known as vesicles) were obtained while hydrating the liquid film with gentle shaking and then with more vigorous shaking. The liposomes which were formed were then suspended in a buffered solution containing calcium and phosphate ions. In some experiments an ionophore, lasalocid acid, sodium salt, was added.

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5. It is clear that the liposomes or vesicles obtained contained phosphate. Indeed it is clear from the reference to ionophore-mediated Ca^{2+} fluxes from the external suspending medium in the Calcif. Tissue article, page 43, right hand column that the purpose of adding the ionophore is to make the liposomes permeable to calcium so that calcium can penetrate the walls of the vesicles and act as a seed for the formation of calcium phosphate on the external surface of the phospholipid walls. There is no suggestion anywhere that I can see that Eanes was able to deposit a layer of calcium phosphate on the outside of the lipid layer without seeding through the vesicle walls.

6. In my experience I can say that the resulting vesicles would have no practical value as carriers for pharmaceutically active compounds which can be released over time, typically as the walls of the vesicles are dissolved by the surrounding medium. This is because the walls of Eanes' vesicles are ruptured by the calcium phosphate. This means that any pharmaceutical present inside the vesicles will leak out in an uncontrolled manner over a short space of time. If vesicles are to be of any real value for the administration of a pharmaceutical agent they must, of course, release the pharmaceutical agent in a predetermined and controlled manner. The vesicles of Eanes cannot do this by virtue of the fact that the membranes are not intact.

I further declare that all statements made herein of my own knowledge are true and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardise the validity of the application or any patent issuing thereon.

29th September 2003

Date

Signature